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Presidential Address, Eighth International Congress of Human Genetics: Human Genetics: The Last 35 Years, the Present, and the Future

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Science is a social enterprise, and these quinquennial convocations are an important part of the sociology of human genetics. They play a role in communication, mutual inspiration, and stimulation that the print and electronic media and other types of meetings, symposia, workshops, and courses, useful as they are, cannot fill. They mark a time to take stock, to look back at what we have accomplished in the last 5 years, but even more to look forward. I shall play Janus and do both.

Let us first look back 35 years to the first of these congresses in Copenhagen in 1956 (fig. 1). At that time, Tjio and Levan, and Ford and Hamerton, were getting the chromosome number right. Newton Morton was writing on linkage analysis. Oliver Smithies was beginning to write on starch gel electrophoresis. Vernon Ingram was narrowing down the molecular defect in sickle hemoglobin to a single peptide, and the first edition of *Heritable Disorders of Connective Tissue* was published. (Please forgive the reference to my own work. I use it as an example of clinical genetics of the period.)

Behold what has happened since then (fig. 2). From the anatomy of the chromosomes at the most elementary level of enumeration, we have gone to their dissection by both mechanical and molecular methods. Genetic linkage has enjoyed a phenomenal renaissance, and now linkage is analyzed on populations of sperm that are studied individually by direct molecular methods. Rather than study variations in proteins by electrophoresis, we now study variation in the DNA itself. From the one example of sickle hemoglobin, the known mutational repertoire of the beta-globin gene has been expanded to over 400. At the DNA level, at least one disease-producing point mutation has been defined in over 170 different genes.

In the heritable disorders of connective tissue, clinical delineation has been refined by molecular definition. For example, in the mucopolysaccharidoses, which in 1956 were lumped under the Hurler syndrome, at least 10 enzymatically distinct entities have been defined, and, in the disorders of the fibrous elements of connective tissue, precise intragenic lesions have been described in osteogenesis imperfecta, in some of the Ehlers-Danlos syndromes and skeletal dysplasias, and, most recently, in the Marfan syndrome.

By the 1961 congress in Rome (fig. 3), clinical chromosomology had arrived. From the findings in the Turner syndrome and the Klinefelter syndrome, the role of the Y chromosome in sex determination was realized; the existence of testis-determining factor (TDF) was deduced. The Lyon hypothesis was the intellectually provocative new concept. Electrophoretic polymorphisms of serum proteins and red cell enzymes were being described. The Philadelphia chromosome was found—one of the first pieces of evidence in humans supporting the chromosome theory of cancer.

Today (fig. 4), imprinting has taken the place of lyonization. TDF has been cloned and characterized under the label SRY (sex-determining region of Y). The fundamental basis of specific forms of cancer has been traced to specific genes—sometimes multiple, sequentially collaborating genes—and to specific mutations within genes.

The Chicago congress in 1966 (fig. 5) was under the presidency of Lionel S. Penrose of the Galton Laboratory in London. The genetic code had been completely

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1956

• Tjio and Levan Ford and Hamerton	correct chromosome number
• Oliver Smithies	starch gel electrophoresis
• Vernon Ingram	molecular difference of sickle hemoglobin
• Newton Morton	lod scores in linkage analysis
• Victor A. McKusick	*Heritable Disorders of Connective Tissue*, 1st ed.

1st International Congress of Human Genetics

Copenhagen

Tage Kemp, President

Figure 1 Some activities in human genetics at time of first congress.

1961

- Clinical 'chromosomology'
  - XO Turner, XXY Klinefelter, etc. --> role of Y in sex determination (TDF)
- Lyon hypothesis
- Genetic polymorphism of serum proteins, red cell enzymes, etc.
- The Philadelphia chromosome in chronic myeloid leukemia

2nd International Congress of Human Genetics

Rome

Luigi Gedda, President

Figure 3 Highlights of second congress

deciphered that year. Somatic cell genetics had entered the scene for the study of inborn errors of metabolism. For example, it provided the strongest proof of the Lyon hypothesis and, through the study of cultured amniotic cells, opened the way for prenatal diagnosis by amniocentesis. The concept of lysosomal diseases had emerged, and the first edition of *Mendelian Inheritance in Man* (MIM), already computer based, was published earlier that year.

I cite MIM because the growth of the successive editions gives me an opportunity to engage in some scientometrics. As the subtitle indicated, MIM was an encyclopedia of phenotypes—genetic traits and disorders. But, from the beginning, it was the intent that there should be one entry per gene locus, based largely on the philosophy that, if two genetic diseases or traits result from mutation at different loci, they are fundamentally distinct however similar in phenotype they may be. Genetics is finding genes—gene hunting. The number of entries in successive editions of MIM can serve as one basis for quantifying progress in our field in the last quarter century. There were about 1,500 entries in the first edition (fig. 6). In the 1960s the only way we had to identify separate entries (read "gene loci") was by Mendelizing phenotypes, sometimes aided by biochemical or immunological characteristics or by genetic features such as linkage. In the 1970s, the rate of accessions was accelerated by a parasexual method for gene identification and mapping, namely, somatic cell hybridization. By the 1980s, cloning of human genes was practiced. Accordingly, entries in MIM were created for genes when they were cloned, sequenced, and mapped, even though no Mendelian

1956	1991
• Correct chromosome number	• Molecular anatomy dissected
• Lod scores (3 autosomal linkages known)	• Extensive genetic linkage maps
• Starch gel electrophoresis of proteins	• Southern blots, etc., of DNA
• Single peptide change in HbS	• >400 mutations in ß globin • >170 genes known with specific disease-producing lesions
• Five major groups of heritable disorders of connective tissue	• Enzymatic delineation of 10 forms of MPS • DNA lesions in OI, EDS, skeletal dysplasias, Marfan syndrome

Figure 2 35 years' progress in human genetics

1961	1991
• TDF	• SRY (sex determining region of Y) cloned = TDF
• Lyon hypothesis	• Imprinting
• Protein polymorphism	• DNA polymorphism
• Ph^1	• Specific DNA changes identified in many cancers

Figure 4 30 years' progress in human genetics

1966

- Genetic code deciphered
- Somatic cell genetics, eg,
  - Proof of Lyon hypothesis
  - Amniocentesis in prenatal diagnosis
- Concept of lysosomal diseases
- *Mendelian Inheritance in Man*, 1st ed.

3rd International Congress of Human Genetics

Chicago

Lionel S. Penrose, President

Figure 5 Highlights of third congress

1971

- Genes assigned to specific autosomes
- Chromosome banding
- Somatic cell genetics, for
  - study of inborn errors of metabolism, eg,
    - -- differentiation of separate mucopolysaccharidoses
    - -- demonstration of HPRT defect in Lesch-Nyhan syndrome
  - chromosome mapping by interspecific somatic cell hybrids

4th International Congress of Human Genetics

Paris

Maurice Lamy, President

Figure 7 Highlights of fourth congress

phenotype had been associated. Today the number of entries (i.e., gene loci) in MIM is over 5,500—still a long way from the 50,000+ expressed genes the human is thought to have.

By the Paris congress in 1971 (fig. 7), the study of inborn errors of metabolism in cultured cells had paid off, for example, with the elucidation of the defect in HPRT in Lesch-Nyhan syndrome and the differentiation of various mucopolysaccharidoses. Chromosome banding had been introduced, and the first genes were being assigned to specific autosomes by linkage to chromosomal heteromorphisms and rearrangements and by interspecies somatic cell hybridization. There were four autosomal assignments by 1971.

The growth of the human gene map since 1971 is my second attempt at scientometrics (fig. 8). By June 1976, just before the 5th Congress in Mexico City, at least one gene had been assigned to every chromosome. This was largely through the application of somatic cell hybridization. By the 1981 congress in Jerusalem, molecular genetic methods for gene mapping had entered the scene and were responsible for further

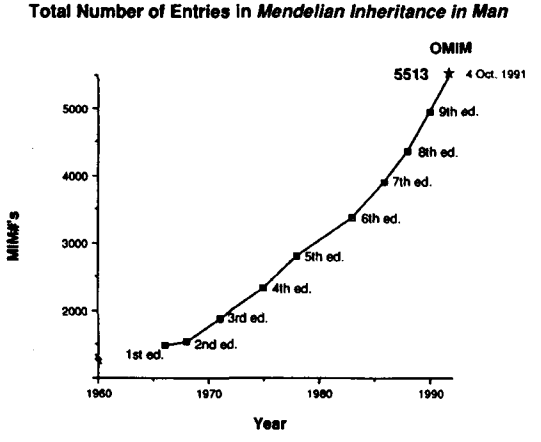

Figure 6 Growth in MIM and its online version (OMIM) over the last 25 years.

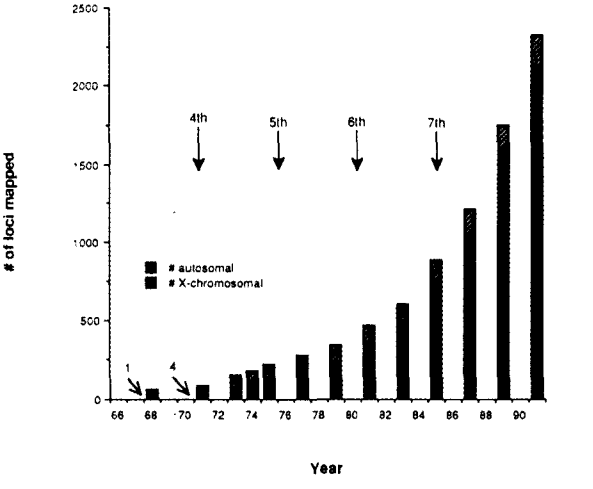

Figure 8 Progress in gene mapping since 1968 when the first assignment of a gene to a specific autosome was achieved. (Arrows indicate the dates of international congresses of human genetics.)

1976

- At least 1 gene mapped to each chromosome
- Concept of receptor diseases, eg,
  -- familial hypercholesterolemia
  -- androgen insensitivity
- Knutson's two-hit hypothesis of hereditary/sporadic tumors
- Reinterpretation of Philadelphia chromsome as translocation

5th International Congress of Human Genetics

Mexico City

Salvador Armendares, President

Figure 9 Highlights of fifth congress

acceleration of mapping in the 1980s. Molecular genetics provided probes for identification of human genes in rodent/human somatic cell hybrids. It provided probes for in situ hybridization to chromosomes; and, importantly, it provided DNA markers (RFLPs, VNTRs, etc.) for family linkage studies, for mapping Mendelian disorders of unknown biochemical basis. Today, a total of at least 2,300 genes have been mapped to specific chromosomes and, for most, to specific chromosomal regions.

By the 5th Congress in Mexico City in 1976 (fig. 9), other advances of note included the concept of receptor diseases—disorders such as familial hypocholesterolemia and androgen insensitivity—and Knudson's two-hit hypothesis of hereditary/sporadic tumors. The Philadelphia chromosome had been reinterpreted as a reciprocal translocation rather than a deletion.

1981

- Human genes cloned
- High resolution cytogenetics
- RFLPs and *in situ* hybridization for gene mapping
- Study of human variation with monoclonal antibodies
- Mitochondrial chromosome sequenced completely

6th International Congress of Human Genetics

Jerusalem

James V. Neel, President

Figure 10 Highlights of sixth congress

1986

- Huntington disease mapped by RFLPs
- New markers: VNTRs
- New techniques: PCR, PFGE, DGGE, CVS
- Transgenic mice expressing human genes
- Genetic basis of antibody diversity elucidated
- "Reverse genetics" - CGD, (DMD)
- Translocations analyzed in CML and Burkitt lymphoma
- Knutson hypothesis proved for retinoblastoma
- Contiguous gene syndromes

7th International Congress of Human Genetics

Berlin

Arno G. Motulsky, President

Figure 11 Highlights of seventh congress

By the 1981 Congress in Jerusalem (fig. 10), in addition to the advances in the methods and results of gene mapping, human genes were being cloned, the genetic basis of antibody diversity was well on the way to elucidation, human variation was being studied with monoclonal antibodies, and one human chromosome was sequenced completely—the mitochondrial chromosome.

1991

- Human Genome Project launched
- Positional cloning: DMD, CF, NF1, APC
- Candidate gene approach to identification of gene defect
  -- retinitis pigmentosa/rhodopsin
  -- hypertrophic cardiomyopathy/cardiac myosin
  -- Marfan syndrome/fibrillin
  -- malignant hyperthermia/ryanodine receptor
- Specific mitochondrial mutations as the basis of disease
- Specific somatic mutations underlying specific cancers
- Imprinting; uniparental disomy

8th International Congress of Human Genetics

Washington

Victor A. McKusick, President

Figure 12 Highlights of eighth congress

Human Genetics

1956-1991

- **medicalized**
- **subspecialized**
- **professionalized**
- **molecularized**
- **consumerized**
- **commercialized**

Figure 13 The "-izing" of human genetics

By 1986 and the congress in Berlin (fig. 11), Huntington disease had been mapped using RFLPs—the first such disorder of unknown biochemical basis mapped by this approach. VNTRs were a new class of markers. PCR had been unveiled at the Cold Spring Harbor meeting of the previous spring. PFGE, DGGE, and CVS were introduced as acronyms for other new techniques or diagnostic methods. Contiguous-gene syndromes were conceptualized and the deletions underlying them used for gene mapping and gene isolation. The approach, which was then called "reverse genetics," had succeeded in isolation of the gene for chronic granulomatous disease and at the very time of the congress was well on the way to characterization of the large gene that is mutant in Duchenne muscular dystrophy. Transgenic mice had been created expressing human genes. The Knudson hypothesis had been proved for retinoblastoma; and the oncogenic molecular changes in the Philadelphia chromosome of chronic myeloid leukemia had been worked out, as well as those in the translocations underlying Burkett lymphoma.

What are the advances of the last 5 years that will be highlighted by this congress of 1991? You will each be making your own list, but here is mine (fig. 12). Certainly, all of us would include the Human Genome Project, which was in a stage of debate and planning in 1986 but by now has been launched. The fruitfulness of positional cloning (alias, reverse genetics) has been established for Duchenne muscular dystrophy, cystic fibrosis, neurofibromatosis, polyposis coli, and others. The candidate-gene approach has also paid off for retinitis pigmentosa, hypertrophic cardiomyopathy, Marfan syndrome, and malignant hyperthermia. The genetics of common cancers such as colon cancer has been greatly elucidated. TDF has been cloned. Specific mutations in the mitochondrial chromosome have been related to specific diseases. Imprinting and uniparental disomy are challenging concepts.

To move from the particular to the general: reflected in the proceedings of these congresses is a continually accelerating pace of scientific advance. The number of attendees at the congresses is a reflection of the growth.

In the last 35 years, human genetics has become *medicalized,* to use Motulsky's term, to an enormous extent. It has become *subspecialized.* Medical genetics has become *professionalized* through the development of clinical colleges and certifying organizations. In the last decade human genetics has also become intensely *molecularized.* Molecular genetics pervades all aspects of human and medical genetics. Human genetics has become *commercialized* to an extent we might not have predicted. The field has also become *democratized* and *universalized;* its implications are felt in all aspects of society. It has become *consumerized;* consumerism is evident in the role of genetic support groups and genetic disease foundations (see fig. 13).

Over the 35 years of the congresses, both new con-

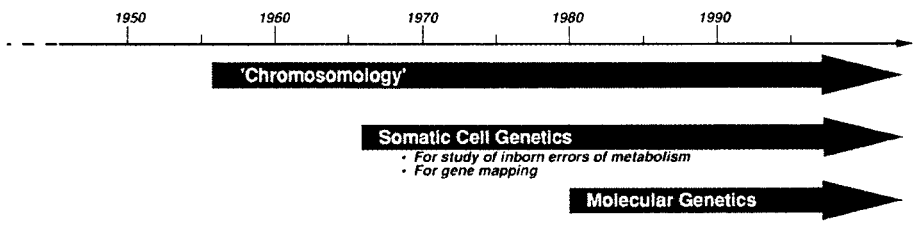

Figure 14 Major methodologies in human genetics I

Genetics - the science of biologic variation.

Human Genetics - the science of biologic variation in the human.

Medical Genetics - the science of human biologic variation as related to health and disease.

Clinical Genetics - that part of medical genetics concerned with disorders in individual patients and their families.
OR
- the science and practice ("art") of diagnosis, prevention, and management of genetic disorders.

Figure 15 Nested definitions

A Source Book for Human Biology and Medicine

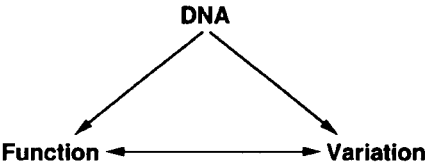

Figure 17 The relation of the product of the HGP to function and variation, and the interrelationship of function and variation.

cepts and new methods have played important roles in progress. One could easily list 5 and perhaps 10 leading concepts that have come along. During that 35 years, three major methodologies have become available successively (fig. 14): chromosomology, starting in 1956; somatic cell genetics—for the study of inborn errors of metabolism and for gene mapping—starting in 1966; and molecular genetics, starting in the human about 1976. (These start dates are obviously somewhat arbitrary; I pick dates of congresses.)

Genetics is the science of biologic variation, and human genetics is the science of biologic variation in the human (fig. 15). In the last 35 years human genetics has moved to progressively more fundamental levels of variation: phenotypic variation, variation in proteins, variation in DNA itself (fig. 16).

In the last few years the *future* of human genetics has been given unprecedented thought and discussion—growing out of the debate over the Human Genome Project and the planning for it. Rarely, if ever, has the future of a scientific field and its implications for society been given such wide and intense attention.

Many take it as a given, that all the genes of the human will be located and sequenced by 2005—some think sooner. This will give a sourcebook of the human (fig. 17) that will be the basis for study in human biology and medicine for a long time to come. When the last gene is found, mapped, and sequenced, we certainly still will not know, for most of them, their function even in solo, let alone in concert with the rest of the genome. True reverse genetics in the New Genetics according to Walter Gilbert, David Botstein, and others will involve working from specific DNA sequences of unknown function to the phenotype. Having in the last 35 years worked progressively from the phenotype to DNA, we will in the next 35 years be returning from DNA to the phenotype by determining the function of specific DNA sequences (fig. 18). Because of its potential for elucidating gene function, may not transgenic technology be a major approach as we move into the era of true reverse genetics (fig. 19)? Just as the function of much of the DNA will remain to be determined when the full sequence is known, the worldwide variation in that DNA will likewise be largely unknown, and long study will be required of the relationship between DNA variation and variation in function (fig. 5)—critical to the understanding of evolution and the genetics of disease susceptibility and performance.

Study of the sourcebook provided by the Human Genome Project should be particularly useful in the

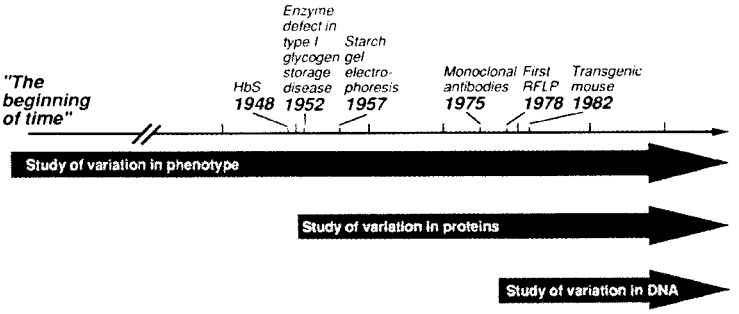

Figure 16 Levels in the study of human variation I

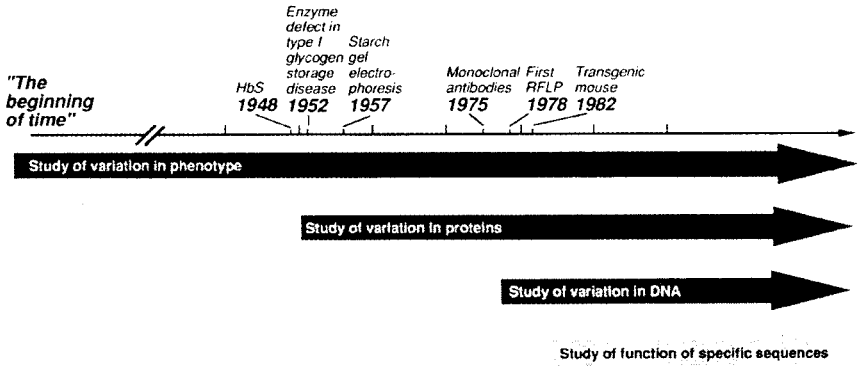

Figure 18 Levels in the study of human variation II

two great frontiers of human biology: How the mind works and how development is programmed. It should be useful in the area of somatic cell genetic disease. Gene mapping and related studies have been primarily responsible for appreciation that in addition to the three classical categories of genetic disease—single-gene disorders, multifactorial disorders, and chromosomal aberrations—somatic cell genetic disease is a large fourth category. This has been most extensively and definitively established through the definition of mutation as the basis of cancer. (Facetiously it is suggested that medical genetics is taking over oncology.) Somatic cell mutations are likely to occupy us increasingly as the basis of congenital malformations, autoimmune processes, and even aging. (McFarlane Burnett suggested about 1960 that somatic cell mutation is the basis of autoimmune processes, and a somatic mutation theory of aging has been entertained for a long time.) The connection between oncogenesis and teratogenesis—between oncogenes and teratogenes, if you will—is already adumbrated by the examples of Wilms tumor and Greig cephalosyndactyly syndrome, to mention two. It is to be assumed that somatic cell gene therapy not only for inherited diseases but perhaps also for some of these acquired somatic cell genetic diseases, especially neoplasia, will become available during the next decade.

Since we met last in Berlin in 1986, extraordinary political changes have taken place on the world scene. The Berlin Wall came down less than 2 years ago. New opportunities opened up for many peoples. Much of the world is in a political revolution. We are in the midst of two scientific and technological revolutions as well: the biological revolution and the information revolution. The two converge in the human genome initiative.

Information is power. Risks can accompany both the political and the scientific changes. Appropriately, ethical, legal, and societal implications of the human genome initiative are being examined in many parts of the world.

The methods developed by the Human Genome Project will allow the rapid and economical generation of information on the genomes of individuals. In the medical area, this information will widen the gap between what we know how to diagnose and what we

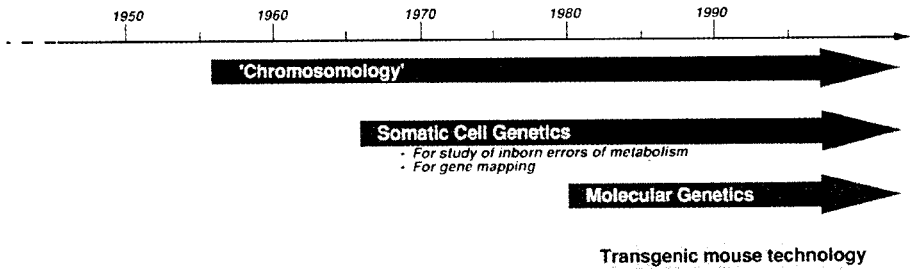

Figure 19 Major methodologies in human genetics II

know how to treat. We already have that problem in the case of Huntington disease. The complete map and sequence is also likely to increase the gap between what we *think* we know and what we *really* know. But by this second gap, I refer in part to the likelihood that weak associations will be found between particular genomic constitutions and certain presumed characteristics such as criminality or alcoholism or elements of intelligence or performance. Some of these associations are likely to be spurious. Other weak associations may be found to be statistically valid but will be blown out of all proper proportions—to the detriment of individuals and of groups. As geneticists we have a responsibility to avoid unfounded conclusions and overblown interpretations and to inculcate profound respect for the genetic variability that is the strength of the species and indeed of the individual—referring to the differences in the two genomes each of us has, one from the father and one from the mother.

The mere existence of the complete reference gene map and DNA sequence down to the last nucleotide may lead to the absurdity of reductionism, the misconception that we then know everything it means to be human, or to the absurdity of determinism, that what we are is a direct and inevitable consequence of what our genome is. Thus, information on the reference gene map and sequence of the human may represent, per se, a hazard, if it distorts the way we think about ourselves and our fellow human beings. The ability to analyze the genomes of individuals is accompanied by risks of information misuse and abuse. We must be alert to the need to protect the privacy and confidentiality of the information that the Human Genome Project will allow to be collected on the genetic constitution of individuals. We must make every effort to avoid the misuse or abuse of such information by third parties, and our governments may need to take measures to assure these protections under law.

President Eisenhower, near the end of his term of office, warned against the dangers of the military/industrial complex. It is appropriate to warn of a potential hazard of the genetical/commercial complex. The increasing availability of tests for presumed genetic quality or disquality could lead the commercial sector and the Madison Avenue publicist to bring subtle or not so subtle pressure on couples to make value judgments in the choice of their gametes for reproduction. Autonomy in reproductive choice is a cornerstone of the ethics of genetic counseling. That reproductive choice would not be autonomous if subjected to the Madison Avenue type of pressure. Especially, trivialization of reproductive choices should be avoided.

As human geneticists we are privileged to work in a scientifically important field and a field of intellectual challenge. Human genetics is a field with particular fascination because it involves the most fundamental and pervasive aspects of our own species—an added fascination that the physical sciences or pure mathematics, for example, cannot share. To have combined with this intellectual and anthropocentric fascination the opportunity to contribute to human welfare and to be of service to families and individuals through medical genetics and clinical genetics (see the definitions in table 12) is a privilege. The privilege carries with it responsibilities to which I have already referred.

This week we celebrate the advances of the recent past and the bright prospect for the future of human genetics. Ladies and gentlemen, as your president, I now declare this 8th International Congress of Human Genetics open.